PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

Pett, Ch.P.
FRANK B. DEHN & CO.
179 Queen Victoria Street
London EC4V 4EL
GRANDE BRETAGNE

FILE 86 69158/001
14 AUG 2000
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NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	11. 08. 2000
Applicant's or agent's file reference 86.89.69158/001	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01388	05/05/1999	05/05/1998

Applicant
WA PHARM AB et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Sinanovic, E Tel.+31 70 340-2672

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
86.89.69158/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01388	05/05/1999	05/05/1998
International Patent Classification (IPC) or national classification and IPC C07K14/685		
Applicant WA PHARM AB et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 7 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/11/1999	11.08.2000
Name and mailing address of the international preliminary examining authority: European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized officer Groenendijk, M Telephone No. +31 70 340 3715

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01388

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-62	as originally filed				
Claims, No.:					
1 (part),4 (part), 5,13-64	as originally filed				
1 (part),2,3,4 (part), 6-12	as received on	16/06/2000	with letter of	16/06/2000	
Drawings, sheets:					
1/6-6/6	as originally filed				

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 30-64 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 30-64 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims 1-64
	No:	Claims
Inventive step (IS)	Yes:	Claims 9
	No:	Claims 1-8,10-64
Industrial applicability (IA)	Yes:	Claims 1-64(see the Separate Sheet)
	No:	Claims

2. Citations and explanations

see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

The corrections made in the claims 2,11 and 12 are considered to be acceptable under Rule 91 PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 30-64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: J.Biol.Chem., Vol.272, 1997, 27943-27948

I.NOVELTY

In view of the available prior art the claims 1-64 are considered to be novel under Art.33(2) PCT.

II.INVENTIVE STEP

1)The closest prior art is considered to be D1 disclosing melanocortin receptor 1 (MCR1) specific peptides obtained by phage display selection having a sequence which is very similar to those disclosed in the claims 1 and 6 (see Table 3) and which compounds have been demonstrated to exhibit a MCR1 modulated biological activity.
2)The compounds of the present application differ from said prior art compounds essentially therein that the C-terminal three amino acid residues are identical to the

corresponding amino acid residues of alpha-MSH. Furthermore some mainly conserved substitutions are allowed in the N-terminal part of the compounds compared to the prior art compounds and the facultative application of usual N-alkylation or backbone modifications to improve the enzymatic resistance have been claimed. According to the experimental data of the examples 2 and 3 at least some of the compounds appear to have an improved affinity to MCR1 and a higher cAMP formation, be it somewhat at the expense of the selectivity for MCR1.

3)The problem to be solved may therefore be considered to be the provision of MCR1 specific peptides having an improved biological activity.

4)It is true that in D1 it was already indicated that the amino acid in position 12 of α-MSH (Pro) is important for the MCR1 binding (see page 27947, column 2). An expert would therefore expect that substitution of Cys by Pro in the sequence MS-04 in table III of D1 would raise the MCR1 binding properties and also solve the instability of the compound due to the Cys sidechain.

However the examiner is of the opinion that the strong increase in binding to MCR1 and in the agonistic activity, while maintaining the high specificity for MCR1, could not be expected on the basis of the teaching of D1. Consequently compounds having said combination of advantageous properties are considered to involve an inventive step under Art.33(3) PCT.

5)At present said advantageous properties have only been demonstrated for the compound MS-05 and to a lesser extent for the compound MS-09. Therefore claim 9 is considered to fulfil the requirements of Art.33(3) PCT.

However from the experimental data of said compounds it appears that only minor structural changes already result in major differences in activity and specificity. The examiner thereof has serious doubts whether all of the novel compounds claimed actually show said advantageous properties and therefore solve the problem posed.

Therefore in order to acknowledge an inventive step under Art.33(3) PCT for the claims 1-8 and 10 and also (having regard to the general prior art concerning the biological activities regulated by MCR1, e.g., see the description on page 2 to page 4) the related claims 11-64, it should be made plausible by additional experimental data that the compounds comprised by that claims actually solve the problem posed.

In this respect it is noted that the mere application of N-alkylation or backbone modification in order to improve the enzymatic stability (claims 3 and 7) is not considered to contribute to the presence of an inventive step.

For the assessment of the present claims 30-64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

The claims 1,6,11 and 12 comprise expressions like "(substituted) (hetero)alkyl", "(substituted) (hetero)aryl" and "amino acid analogue", which expressions are open-ended, rendering the scope of the claims unclear under Art.6 PCT.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01388

Box I Observations where certain claims wer found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 31-64
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claims 31-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01388

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/685 C12N15/16 A61K38/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SZARDNINGS E.A.: "Phage display selection on whole cells yields a peptide specific for melanocortin receptor 1" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 44, 31 October 1997 (1997-10-31), pages 27943-27948, XP002113068 MD US cited in the application the whole document	1-64

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1999	03/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

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Form PCT/ISA/210 (second sheet) (July 1992)

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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CI	Côte d'Ivoire	KP	Democratic People's Republic of Korea	NZ	New Zealand		
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CN	China	KR	Republic of Korea	PT	Portugal		
CU	Cuba	KZ	Kazakstan	RO	Romania		
CZ	Czech Republic	LC	Saint Lucia	RU	Russian Federation		
DE	Germany	LI	Liechtenstein	SD	Sudan		
DK	Denmark	LK	Sri Lanka	SE	Sweden		
EE	Estonia	LR	Liberia	SG	Singapore		

PATENT COOPERATION TREATY

PCT

REC'D 14 AUG 2000
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
86.89.69158/001		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB99/01388	05/05/1999	05/05/1998
International Patent Classification (IPC) or national classification and IPC		
C07K14/685		
Applicant		
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   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
04/11/1999	11.08.2000
Name and mailing address of the international preliminary examining authority:	Authorized officer
European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Groenendijk, M Telephone No. +31 70 340 3715

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB99/01388

I. Basis of th report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

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1-62	as originally filed				
Claims, No.:					
1 (part),4 (part), 5,13-64	as originally filed				
1 (part),2,3,4 (part), 6-12	as received on	16/06/2000	with letter of	16/06/2000	
Drawings, sheets:					
1/6-6/6	as originally filed				

2. The amendments have resulted in the cancellation of:

☐ the description, pages:
☐ the claims, Nos.:
☐ the drawings, sheets:

3. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claim d invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 30-64 with respect to industrial applicability.

because:

☒ the said international application, or the said claims Nos. 30-64 relate to the following subject matter which does not require an international preliminary examination (*specify*):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-64
	No:	Claims	
Inventive step (IS)	Yes:	Claims	9
	No:	Claims	1-8,10-64
Industrial applicability (IA)	Yes:	Claims	1-64(see the Separate Sheet)
	No:	Claims	

2. Citations and explanations

see separate sheet

VIII. Certain observations on the int rnational application

The following observations on the clarity of the claims, description, and drawings or on the question whether th claims are fully supported by the description, are made:

see separate sheet

Re Item I

Basis of the opinion

The corrections made in the claims 2,11 and 12 are considered to be acceptable under Rule 91 PCT.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 30-64 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following document:

D1: J.Biol.Chem., Vol.272, 1997, 27943-27948

I.NOVELTY

In view of the available prior art the claims 1-64 are considered to be novel under Art.33(2) PCT.

II.INVENTIVE STEP

1)The closest prior art is considered to be D1 disclosing melanocortin receptor 1 (MCR1) specific peptides obtained by phage display selection having a sequence which is very similar to those disclosed in the claims 1 and 6 (see Table 3) and which compounds have been demonstrated to exhibit a MCR1 modulated biological activity.
2)The compounds of the present application differ from said prior art compounds essentially therein that the C-terminal three amino acid residues are identical to the

corresponding amino acid residues of alpha-MSH. Furthermore some mainly conserved substitutions are allowed in the N-terminal part of the compounds compared to the prior art compounds and the facultative application of usual N-alkylation or backbone modifications to improve the enzymatic resistance have been claimed. According to the experimental data of the examples 2 and 3 at least some of the compounds appear to have an improved affinity to MCR1 and a higher cAMP formation, be it somewhat at the expense of the selectivity for MCR1.

3)The problem to be solved may therefore be considered to be the provision of MCR1 specific peptides having an improved biological activity.

4)It is true that in D1 it was already indicated that the amino acid in position 12 of α-MSH (Pro) is important for the MCR1 binding (see page 27947, column 2). An expert would therefore expect that substitution of Cys by Pro in the sequence MS-04 in table III of D1 would raise the MCR1 binding properties and also solve the instability of the compound due to the Cys sidechain.

However the examiner is of the opinion that the strong increase in binding to MCR1 and in the agonistic activity, while maintaining the high specificity for MCR1, could not be expected on the basis of the teaching of D1. Consequently compounds having said combination of advantageous properties are considered to involve an inventive step under Art.33(3) PCT.

5)At present said advantageous properties have only been demonstrated for the compound MS-05 and to a lesser extent for the compound MS-09. Therefore claim 9 is considered to fulfil the requirements of Art.33(3) PCT.

However from the experimental data of said compounds it appears that only minor structural changes already result in major differences in activity and specificity. The examiner thereof has serious doubts whether all of the novel compounds claimed actually show said advantageous properties and therefore solve the problem posed.

Therefore in order to acknowledge an inventive step under Art.33(3) PCT for the claims 1-8 and 10 and also (having regard to the general prior art concerning the biological activities regulated by MCR1, e.g., see the description on page 2 to page 4) the related claims 11-64, it should be made plausible by additional experimental data that the compounds comprised by that claims actually solve the problem posed.

In this respect it is noted that the mere application of N-alkylation or backbone modification in order to improve the enzymatic stability (claims 3 and 7) is not considered to contribute to the presence of an inventive step.

For the assessment of the present claims 30-64 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item VIII

Certain observations on the international application

The claims 1,6,11 and 12 comprise expressions like "(substituted) (hetero)alkyl", "(substituted) (hetero)aryl" and "amino acid analogue", which expressions are open-ended, rendering the scope of the claims unclear under Art.6 PCT.

$-CH_2X$, where X is H, alkyl, substituted alkyl, heteroalkyl, substituted heteroalkyl, alkenyl, substituted alkenyl, heteroalkenyl, substituted heteroalkenyl, alkynyl, substituted alkynyl, heteroalkynyl, substitut d heteroalkynyl, cycloalkyl, substituted cycloalkyl, cycloheteroalkyl, substituted cycloheteroalkyl, cycloalkenyl, substituted cycloalkenyl, cycloheteroalkenyl, substituted cycloheteroalkenyl, aryl, substituted aryl, heteroaryl, substituted heteroaryl, functional group,

and wherein NT is selected from H, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide and functional group, and CT is selected from hydrogen, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide and functional group, and wherein each asymmetric center (*) is in R or S configuration;

the compound optionally possessing one or several of the following properties:

a) showing high affinity for MC1 receptors, and/or

b) showing high selectivity for MC1 receptors, and/or

c) showing high capacity to stimulate the second messenger cAMP, and/or,

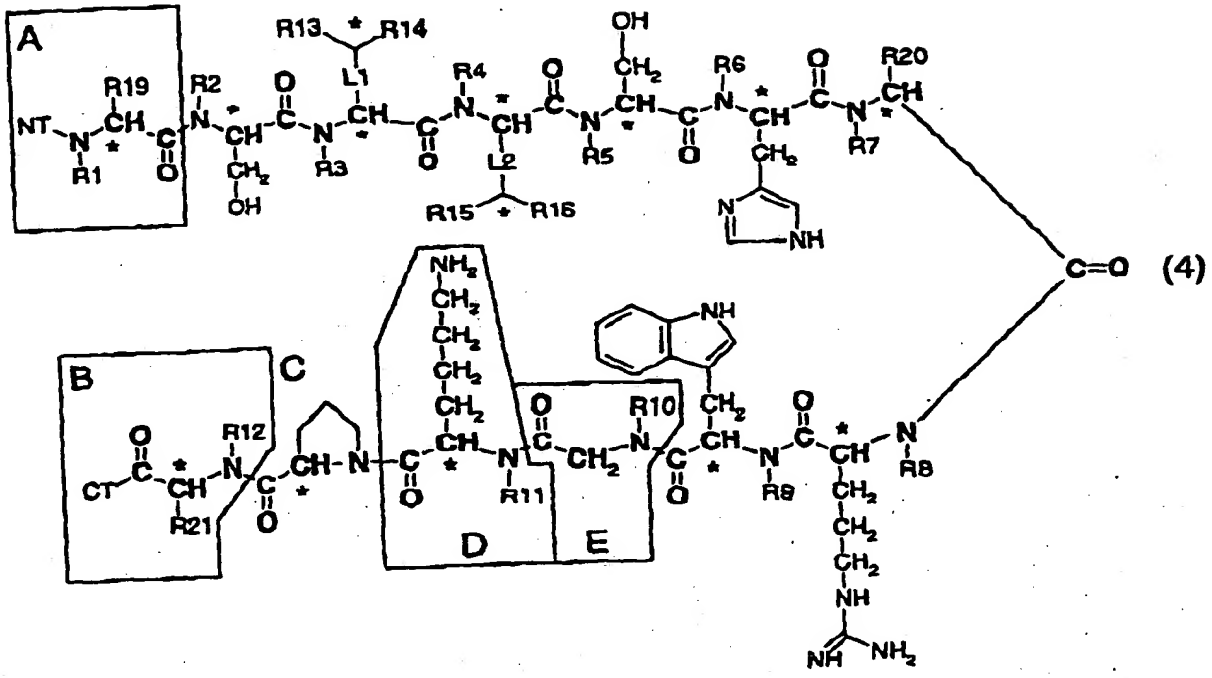
d) being an effective inhibitor of NO production.

2. The compound of claim 1, wherein R20 is $-CH_2X$, wherein X is phenyl.

3. The compound of claim 1 or 2, wherein one or several of the nitrogens of the peptide backbone have been exchanged for carbon substituted with hydrogen, and/or wherein one or several of the oxygens of the carbonyl groups of the peptide backbone has been exchanged for two hydrogens.

4. The compound of any one of claims 1 to 3, having the stereomeric conformation given in the general formula (2):

6. A compound of the general formula (4):



wherein R1 to R16, R19 to R21, NT and CT are as defined in claim 1,

wherein moiety A is optionally exchanged for hydrogen, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide, or functional group,

wherein moiety B is optionally exchanged for hydrogen, hydroxyl, alkyl, aminoacid, aminoacid analogue, polypeptide, or functional group,

wherein optionally moiety D is exchanged for aminoacid or aminoacid analogue,

and wherein optionally moiety E is exchanged for aminoacid or aminoacid analogue.

7. A compound according to any one of claims 1-4 or 6, wherein one or several of R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 are selected to be methyl, whereas the rest is selected to be hydrogen, the selections being made so as to prevent or decelerate breakdown by proteases and/or peptidases.

AMENDED SHEET
IPEA/EP

8. A compound according to any one of claims 1-4 or 6, wherein l ss than 6, preferably less than 5, more preferred less than 4 and preferably less than 2, and most preferred none of the R1, R2, R3, R4, R5, R6, R7, R8, R9, R10, R11 and R12 are methyl.

9. A compound comprising the sequence Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (SEQ ID NO:1), wherein the amino-acids are all L-amino-acids.

10. A compound comprising one of the followings sequences:

Ser-Ser-Ile-Ile-Ser-His-dPhe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-09) (SEQ ID NO:2)
Tyr-Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-30) (SEQ ID NO:3)
Tyr-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-31) (SEQ ID NO:4)
Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Tyr-NH_2 (MS-32) (SEQ ID NO:5)
Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-33) (SEQ ID NO:6)
Thr-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-34) (SEQ ID NO:7)
Ser-Thr-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-35) (SEQ ID NO:8)
Ser-Ser-Val-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-36) (SEQ ID NO:9)
Ser-Ser-Ile-Val-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-37) (SEQ ID NO:10)
Ac-Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-38) (SEQ ID NO:11)
dSer-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-39) (SEQ ID NO:12)
NMeSer-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-40) (SEQ ID NO:13)
Ser-Ser-Ile-Ile-Ser-His-Phe-Arg-Trp-Gly-Lys-Pro-NMeVal-NH_2 (MS-41) (SEQ ID NO:14)
Ser-Ser-Ile-Ile-Ser-His-NMedPhe-Arg-Trp-Gly-Lys-Pro-Val-NH_2 (MS-42) (SEQ ID NO:15)

11. A compound according to any one of claims 1-4 or 6-8, in which R20 is -CH_2X, wherein X is aryl, substituted aryl, heteroaryl, substituted heteroaryl, phenyl or substituted phenyl, or a compound according to any one of claims 5, 9 or 10, wherein the compound is capable of activating MC1-receptors.

12. A compound according to any one of claims 1-4 or 6-8, in which R20 is -CH_2X, wherein X is aryl, substituted aryl, heteroaryl, substituted heteroaryl, naphthalene, or substituted naphthalene, or a compound according to any one of claims 5, 9 or 10, wherein the compound is capabl of bl cking MC1-receptors.

AMENDED SHEET
IPEA/EP

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
86.89.69158/001		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 99/01388	05/05/1999	05/05/1998
Applicant		
WA PHARM AB et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

[ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

[X] contained in the international application in written form.

[X] filed together with the international application in computer readable form.

[ ] furnished subsequently to this Authority in written form.

[ ] furnished subsequently to this Authority in computer readble form.

[ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

[ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

[X] the text is approved as submitted by the applicant.

[ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

[ ] as suggested by the applicant.

[ ] because the applicant failed to suggest a figure.

[ ] because this figure better characterizes the invention.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 99/01388

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 31-64
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claims 31-64 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 99/01388

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/685 C12N15/16 A61K38/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SZARDNINGS E.A.: "Phage display selection on whole cells yields a peptide specific for melanocortin receptor 1" JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 272, no. 44, 31 October 1997 (1997-10-31), pages 27943-27948, XP002113068 MD US cited in the application the whole document	1-64

☐ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
24 August 1999	03/09/1999

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Groenendijk, M

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Form PCT/ISA/210 (second sheet) (July 1992)

ATENT COOPERATION TRE Y

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

PETT, Christopher, Phineas
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4 4EL
ROYAUME-UNI

Date of mailing (day/month/year)
31 October 2000 (31.10.00)

Applicant's or agent's file reference
86.89.69158/001

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/01388

International filing date (day/month/year)
05 May 1999 (05.05.99)

1. The following indications appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address
WA PHARM AB
c/o Melacure Therapeutics AB
Uppsala Science Park
S-751 83 Uppsala
Sweden

State of Nationality: SE
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
WA PHARM AB
c/o Melacure Therapeutics AB
Ulleråkersvägen 38
S-756 43 Uppsala
Sweden

State of Nationality:
State of Residence:
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

Authorized officer
Peggy Steunenberg
Telephone No.: (41-22) 338.83.38

Copy for the Elected Office (EO/US) PCT/GB99/01388

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

PETT, Christopher, Phineas
Frank B. Dehn & Co.
179 Queen Victoria Street
London EC4 4EL
ROYAUME-UNI

Date of mailing (day/month/year)
31 October 2000 (31.10.00)

Applicant's or agent's file reference
86.89.69158/001

IMPORTANT NOTIFICATION

International application No.
PCT/GB99/01388

International filing date (day/month/year)
05 May 1999 (05.05.99)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address
MUCENIECE, Ruta
Sernanders väg 3
S-752 61 Uppsala
Sweden
Sweden

State of Nationality: LV
State of Residence: SE
Telephone No.:
Facsimile No.:
Teleprinter No.:

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address
MUCENIECE, Ruta
Sernanders väg 3/333
S-752 61 Uppsala
Sweden
Sweden

State of Nationality:
State of Residence:
Telephone No.:
Facsimile No.:
Teleprinter No.:

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Peggy Steunenberg

Telephone No.: (41-22) 338.83.38

Form PCT/IB/306 (March 1994) 003622071

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 24 November 1999 (24.11.99)	
International application No. PCT/GB99/01388	**Applicant's or agent's file reference** 86.89.69158/001
International filing date (day/month/year) 05 May 1999 (05.05.99)	**Priority date** (day/month/year) 05 May 1998 (05.05.98)
Applicant SZARDENINGS, Michael et al	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

04 November 1999 (04.11.99)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38